REMARKS

The term synuclein-NAC has been changed to NAC fragment of alpha-synuclein as described at *e.g.*, p. 19, lines 28-29. No change in meaning is meant by this amendment, and it should not be construed as acquiescence in any ground of rejection. Applicant responds to the office action using the paragraph numbering of the office action.

¶5. The priority claim currently in the PTO system is incorrect. A Supplemental ADS with a corrected priority claim is being submitted here with and the cross-reference to related application is being amended. As well as the immediate parent, US Application No. 09/585,817, filed June 1, 2000, which has identical disclosure to the present application, priority is claimed to US Application No. 09/580,015, which discloses antibodies to NAC at *e.g.*, p. 98, lines 3-6 and US Application No. 60/137,101, filed June 1, 1999, which discloses active and passive regimes using NAC and antibodies thereto (*see, e.g.*, p. 5, lines 10-11 and claim 39, respectively). Thus, the present application is entitled to a priority of at least June 1, 1999.

¶6. The Examiner alleges that the present claims are not enabling for methods of therapeutic or prophylactic treatment of Alzheimer's disease. The Examiner's position is in part based on the allegation that the specification does not disclose examples showing a reduction of the severity of symptoms. However, the specification does provide examples showing that antibodies to Aβ can reduce amyloid deposits in a transgenic model of Alzheimer's deposits. Because these deposits are the principal pathology associated with Alzheimer's disease, it is expected that removal of the deposits is associated with corresponding benefit in symptoms of a treated patient. Indeed, such a benefit has been shown in a human clinical trial as described in an attached declaration by Dr. Martin Koller. Although the clinical trial was conducted on full-length Aβ rather than the antibodies at issue here, the trial is relevant is showing that the data obtained in the transgenic mouse model are predictive of cognitive benefits in humans. In other words, because antibodies to Aβ show similar results to Aβ peptide in a transgenic animal model, they are expected to in a human too.

As the Examiner has noted the specification provides a working example showing that an antibody to the NAC fragment of alpha synuclein can achieve similar results to antibodies

to Aβ in an *ex vivo* model. The results for antibodies to Aβ in the *ex vivo* model closely track *in vivo* performance of the antibodies in clearing amyloid deposits (Table 16). Thus, one would expect similar results from the antibody to NAC. In any event, one would not expect that a combination of an antibody to Aβ and an antibody to NAC would be less effective than an antibody to Aβ itself.

Insofar as the Examiner is suggesting that results in a model system of Alzheimer's disease are insufficient to support enablement, the issues raised are similar to those considered in *In re Brana,* 34 USPQ2d 1436 (Fed. Cir. 1995). The *Brana* court reversed a rejection under 35 U.S.C. § 112, first paragraph based on the PTO's refusal to accept data from testing compounds in an animal model of cancer (*Id.* at 1444). The animal model at issue in *Brana* was formed by injecting cancer cells into mice. The PTO took the position that the model was not fully representative of human cancers because the mice did not naturally develop cancers (*Id.* at 1440). The PTO argued that "*in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, [meaning] *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans" (*Id.* at 1142). The Federal Circuit reversed the rejection as "arbitrary and capricious." The Federal Circuit held that "Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings" (*Id.* at 1442).

The Examiner also faults the term "prophylaxis" as including prevention on the basis that the art allegedly recognizes that prophylactic treatment of Alzheimer's disease is essentially impossible. Assuming *arguendo* that the claimed methods cannot completely prevent (or cure) Alzheimer's disease, they would be no different than many other highly successful drugs. For example, it is well know that the success of "blockbuster" cancer drugs is measured in increments of extending the life of a patient for a few months, a result far removed from total cure or prevention. In these circumstances, applicant submits that with the presently claimed methods as in other patents claiming methods of treatment or prophylaxis, the possibility that the methods may not achieve a total cure or prevention is not detrimental to enablement and need not be excluded from the claims. Enablement does not require that generic claims function in every

conceivable circumstance. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.* 224 USPQ 409 (Fed. Cir. 1984).

In the event that Examiner persists with this rejection, applicant also requests clarification from the Examiner if any alternative language in the claims would address his concerns. For example, the concept of prophylaxis could also be recited in terms of delaying or inhibiting onset of Alzheimer's disease in a patient susceptible to the disease, and therapeutic treatment could be expressed simply as treatment of a patient suffering from Alzheimer's disease. Alternatively, is the Examiner seeking language that explicitly excludes the possibility of total cure or prevention? If the latter, applicant respectfully submits that this is an unreasonable requirement that is rarely, if ever, insisted on in patents claiming methods of treatment or prophylaxis notwithstanding that the capacity of such methods to effect total cure or prevention of a disease would almost always be, at best, unknown.

Next, the office action alleges the specification does not provide examples for use of antibodies to NAC in an animal model, and alleges that the *ex vivo* model is unreliable. However, the Examiner has not provided any reasons that the *ex vivo* model is unreliable. In particular, the Examiner has not addressed the evidence provided by Table 16 that the *ex vivo* model provides excellent correlation between the capacity of antibodies to Aβ to clear amyloid deposits *ex vivo* and *in vivo*. Because both Aβ and NAC are components of such deposits, would expect a similar correlation for antibodies to NAC.

Next the Examiner alleges that applicant has not identified the appropriate specificity of antibody within NAC. However, applicant has provided a simple *ex vivo* screen that allows the skilled person to test whether any given antibody to NAC is effective in clearing deposits. The availability of such a screen allows suitable antibodies to be identified without undue experimentation. The situation is analogous to *In re Wands,* 8 USPQ2d 1400 (CAFC 1988The issue in *Wands* was whether the specification of the *Wands* patent enabled production of a class of antibodies having IgM isotype and a binding affinity of at least 10^9 M^{-1} using the Kohler-Milstein technology. The Kohler-Milstein technology is a classic technique that involves individualized screening of hybridomas to identify a subset with desired binding characteristics. Until the hybridomas have been screened, it is unpredictable which will have the desired

characteristics. The evidence indicated that only some of the hybridomas to be screened would produce antibodies having the desired property. Nevertheless, the court found that "practitioners of this art are prepared *to screen negative hybridomas in order to find one that makes the desired antibody*" (858 F.2d at 740, emphasis supplied). The *Wands* patent was held to be enabled.

The Examiner also alleges that the specification does not say whether the exemplified antibody was chimeric, humanized or human. However, such has little relevance, because any of these antibodies can be screened by the above method.

Next the Examiner alleges additional difficulties from the claims including antibodies to forms of synuclein other than alpha synuclein or synuclein fragments other than NAC. However, the term "NAC" is one of art used to refer to a fragment of alpha synuclein present in plaques. Thus, the term "synuclein-NAC" inherently means the NAC fragment of alpha synuclein. There is no NAC fragment of beta or gamma synuclein. Nevertheless, the claims have been amended to specify explicitly that a NAC fragment of alpha synuclein is intended.

¶7. Claims 11, 58, and 74-81 stand rejected for lack of written description on the basis that the disclosure of a single antibody does not support the claimed genus. In response, this rejection appears to reflect at in least in large part the same issue of interpretation just discussed. That is, the term "synuclein-NAC" means the NAC fragment of alpha synuclein.

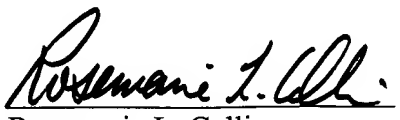
Insofar as the rejection is maintained notwithstanding the above amendment, applicant notes that the present claims differ from those at issue in *Eli Lilly vs. University of California* in that the invention lies not in *de novo* isolation of a gene but in provision of antibodies to a well-characterized target (*i.e.*, a NAC fragment of alpha synuclein). In circumstances in which the invention lies in cloning a gene, it is perhaps not unreasonable that a newly isolated gene cannot be described without determining its sequence. However, the PTO's Guidelines for application of the written description requirement explicitly recognize that a class of antibodies can be defined in functional terms without providing sequence data. The functional definition of an antibody is sufficient because of "the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the

antibody technology is well developed and mature." *See* Example 6 of the Synopsis of Application of Written Description Guidelines. In keeping with these guidelines, numerous patents have issued in which antibodies are characterized in part or in whole by functional properties, such as binding affinity. For example, the antibodies in *Wands* are characterized by the property of a binding affinity of at least $10^9 M^{-1}$ for a target antigen.

¶¶8-9. Claims 11, 58, 74-75 and 78-79 stand rejected as allegedly obvious over Masliah in view Schenk, US 6,710,225 or WO 99/27944. Applicant initially notes that Masliah twice expresses doubt that antibodies can cross the blood brain barrier (p. 5 last paragraph and p. 41 last paragraph). More importantly, however, neither Schenk reference is prior art. Schenk, US 6,710,225 is not prior art under 35 U.S.C. § 102(e) because of common inventorship with the present case. Schenk, WO 99/27944 is not prior art under 35 U.S.C. § 102(a) because of common inventorship with the present case, and is not prior art under 35 U.S.C. § 102(b) because it was published less than a year before the June 1, 2000. The Examiner does not dispute that applicant is entitled at least to the priority of this date (office action at p. 3, first paragraph). Because neither Schenk reference is prior art, a prima facie case of obviousness has not been established.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-625-8100.

Respectfully submitted,



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MOUNTAIN VIEW OFFICE
23493
CUSTOMER NUMBER

Date: February 21, 2006
35455-1